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Formulation, *In Vitro* Evaluation and Stability Studies of Oral Disintegrating Films of Candesartan Cilexetil

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Abstract
Candesartan Cilexitil is an Angiotensin II receptor antagonist used in the treatment of hypertension. But it exhibits poor water solubility and extensive first pass metabolism. This study aims to focus on development of oral disintegrating films containing solid dispersions of Candesartan Cilexetil with an objective of improving its water solubility and offering a rapid as well as a prolonged delivery coupled with enhanced therapeutic efficacy, patient compliance and the bioavailability. First the solid dispersions were prepared by fusion method using mannitol as a carrier in different ratios of 1:1, 1:2, and 1:3. Then oral disintegrating films of candesartan were prepared by solvent casting method using film forming polymers like PVA, HPMC-E5 and sodium alginate of different concentrations. Prepared films were evaluated for their Weight, Thickness, Surface pH, Drug content uniformity, *in vitro* disintegration time, folding endurance, in vitro drug release and stability studies. Six formulations were prepared of which F3 formulation containing HPMC-E5 was found to be as optimised with in vitro drug release of 98.91±0.73% within 10 mins and disintegration time of 21.33±1.52 secs. Results from stability studies indicate that the formulated oral disintegrating films are stable and no remarkable changes were observed.

Keywords
Candesartan cilexetil, solid dispersions. Oral disintegrating films, fusion method, solvent casting method.

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INTRODUCTION
Oral administration is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. However oral drug delivery systems still need some advancements to be made because of some drawbacks related to particular class of patients which includes geriatric, paediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many paediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking [1].
Research and development in the Oral drug delivery technology has improved from conventional dosage forms to modified release dosage forms to oral disintegrating tablet to the recent development of oral fast disintegrating films (OFDFs). Most ODTs are fragile and brittle, which need special package for

protection during storage and transportation. But the films are flexible, they are not as fragile as ODTs, easy transportation, handling and storage [2].

Oral disintegrating film or strip can be defined as a dosage form that employs a water dissolving polymer which allows the dosage form to quickly hydrate by saliva, adhere to mucosa, and disintegrate within a few seconds, dissolve and releases medication for Oro-mucosal absorption when placed on the tongue or oral cavity. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances [1].

Candesartan is an angiotensin II receptor blocker (ARB). ARBs are widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Candesartan is an orally active non-peptide tetrazole derivative. It finds most significant clinical use in the treatment of hypertension of all grades. Candesartan is a potent, highly selective ARB that is devoid of agonist activity. Candesartan cilexetil is an ester prodrug of its active metabolite Candesartan, to which it owns its therapeutic effect. It is also used in the treatment of congestive heart failure. Candesartan is used experimentally in preventive treatment of migraine [3].

MATERIALS AND METHODS

Candesartan cilexetil is a gift sample from Hetero Labs Pvt Ltd Hyderabad, mannitol, HPMC-E5, PVA, Sodium alginate, propylene glycol, citric acid and aspartame are collected from S.D Fine Chem. Ltd. Mumbai.

Preformulation Studies:

1.Solubility Determination: The solubility of Candesartan cilexetil was determined using saturation solubility method. An excess amount of Candesartan cilexetil was added to 10 ml of distilled water, phosphate buffer pH 6.8, pH-7.2 and methanol in conical flask. The samples were shaken for 48 hrs in a rotary shaker. The solution was filtered through 0.45 µ membrane filter and then. Accurately measured 0.5 ml of the filtrate was immediately diluted with sufficient amount of the same solvent and analysed spectrophotometrically using UV-visible spectrophotometer at 254 nm after suitable dilution [4,5].

Drug Excipients Compatibility Studies:

1.Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR spectra of pure Candesartan Cilexetil, and mixture of drug and excipients were recorded using FTIR spectrophotometer to study the incompatibility over the wavelength range of 400–4000/cm by preparing a dispersion of samples in KBr [4].

2.Differential Scanning Calorimetric (DSC):

DSC-Thermogram, Candesartan cilexetil, and mixture of drug with excipients were recorded using DSC to study the incompatibility. All samples were weighed and heated in a closed pierced aluminium pan at a scanning rate of 10 °C/min between 30 °C-300 °C and 60 ml/min of nitrogen flow [6].

Preparation of Physical Mixtures (PMs)

Physical mixtures were obtained by uniform mixing of drug and carrier in 1:1, 1:2 and 1:3 ratios. The solid mass was then pulverized in glass mortar. The resultant product was passed through a sieve of 80 mesh size to get uniformly sized particles [6].

Preparation of Candesartan Cilexetil Solid Dispersions Using Melting Method:

In melting method, required quantity of the drug with mannitol, were prepared in the ratio of 1:1, 1:2 and 1;3 mixed well in a china dish and heated up to a temperature just beyond the melting points of the carriers. The system was placed in an ice bath until solidification occurred. The mass was crushed, ground with a mortar and pestle and passed through 30 mesh sieve [7].

Characterization of Solid Dispersions:

1. Drug Content

10 mg of solid dispersions and physical mixtures were weighed accurately and dissolved in 10 ml of 6.8 pH buffer. The solution was filtered, diluted suitably and drug content was analysed by UV spectrophotometer. Actual drug content was calculated for all batches using the equation as follows [8].

Percentage of drug content = observed value/actual value × 100

2. Saturation Solubility Studies

test was carried out to determine solubility of Candesartan cilexetil in presence of carrier mannitol. This was done by dissolving excess amount of drug in flasks containing different concentrations of carrier in different ratios (1:1, 1:2 and 1:3) in distilled water. The flasks were shaken thoroughly at 200rpm and kept aside for 48hours. The suspensions were filtered and absorbance was measured at 254nm after dilution [7].

3. *In Vitro* Drug Release Studies

In vitro release profile for each solid dispersion as well as pure drug was performed using USP type 2

dissolution apparatus. Sample equivalent to 10 mg of candesartan cilexetil was added to 900ml of phosphate buffer of pH 6.8 at 37±0.5˚C and stirred at 75 rpm. Aliquot of 5 ml was withdrawn at time intervals of 15, 30, 45 and 60 min. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} (254nm) after suitable dilution if necessary, using appropriate blank [8].

Preparation of Fast Dissolving Films

Fast dissolving films of candesartan cilexetil were prepared using solvent casting method. The required amount of film forming polymer was accurately weighed, dispersed in distilled water and soaked aside for 1hour for swelling of polymer. Accurately weighed quantity candesartan cilexetil solid dispersion, propylene glycol which is used as a plasticizer, Citric acid as saliva stimulating agent, menthol (flavoring agent) and aspartame (sweetener) were dissolved in distilled water in another beaker.

After complete hydration of the polymer with water, drug solution was added to the polymer solution and mixed thoroughly with magnetic stirrer. The resulting solution was sonicated for 20 min for removal of air bubbles. The bubble free solution was casted on to a Petri dish of 9.7cm diameter which was placed over a flat surface. Funnel was inverted over petri dish and kept for 24 hours at room temperature for drying. The film was removed from the Petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Film was cut into (2x2 cm^2) and wrapped in an aluminium foil and stored in desiccators [6]. Amount of the polymers used for the development of films is given in Table-1.

Evaluation of Fast Dissolving Films:

1.Film Thickness:

The film thickness can be measured by micrometer screw gauge at 5 different locations (one at center and four corners of the film), and the average value was calculated. This is essential to determine uniformity in the film thickness which is subsequently related to the accuracy of dose in the film. The thickness of film should be in the range of the 5-200 micrometer [6].

2.Weight Variation:

Weight variation was studied by individually weighing 10 randomly selected films and calculating the average weight. According to specifications given in I.P. 2007 for 45 mg film standard deviation should not more than 10% [9].

3.Surface pH

One film (2x2 cm^2) of each formulation was transferred into a petri dish and moistened with 1 ml of distilled water and kept for 1 h. surface pH was measured by bringing the electrode of the pH meter in contact with the surface of the film and allowing it to equilibrate for 1 min. A mean of three readings and standard deviation was recorded [6].

4.Folding Endurance

The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This gives the indication of brittleness of the film. A strip of 2x2 cm^2 was subjected to this test by folding the film repeatedly at the same plane for several times until a visible crack was observed, and the values were reported [6].

5. *In Vitro* Disintegration Time:

Candesartan cilexetil films (2x2 cm^2) of each formulation were allowed to disintegrate by putting them in a 20 ml of phosphate buffer pH 6.8 in glass petri plate with mild agitation. The time at which film starts to break or disintegrates completely was noted as disintegration time with stopwatch [10].

6.Percentage Drug Content

Candesartan Cilexetil films (2x2 cm^2) were transferred into separate volumetric flasks containing 100 ml of phosphate buffer pH 6.8. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution. The samples were filtered, diluted, and analysed for percentage drug content by double beam UV visible spectrophotometer.

7.*In Vitro* Drug Dissolution

The *in vitro* drug dissolution test of film (2x2 cm^2) was carried out using USP type 1 dissolution apparatus. The dissolution medium comprised 300 ml of phosphate buffer pH 6.8 maintained at a temperature of 37 ± 0.5°C and rotation speed of 50 rpm was kept. During the study, 2 ml of samples were withdrawn at 2, 4, 6, 8 and 10mins and the samples were replaced by fresh buffer to maintain sink conditions. The drug concentration was measured by a UV Spectrophotometer [8,4].

8.Study of Release Kinetics:

In order to determine the drug release mechanism that provides the best description to the pattern of drug release, the in vitro release data were fitted into various model dependent methods such as zero order, first order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas model. The release data was fitted to following mathematical models like [11]:

Zero-order kinetic: $Qt=Q_0+k_0t$

Where, Qt is amount of drug release at time t; K_0 is zero order release rate constant; Q_0 is amount of drug present initially at t=0.

First-order kinetic: $\ln (100-Q) = \ln Q_0 - K_1t$

Where, Q=amount of drug present initially; K_1=first order release rate constant.

Higuchi equation: $Q=kH\ t_{1/2}$

Where, $t_{1/2}$=amount of drug release at time t; kH=Higuchi dissolution constant.

Korsmeyer-Peppas model: $Q=Kpt^n$

Where, Kp is a constant incorporating the structural and geometric characteristics of the drug dosage form.

Hence to study the drug release kinetics data obtained from in-vitro dissolution study. The data obtained is plotted against:

- Time vs.% CDR for Zero order kinetics;
- Time vs. Log% drug remaining for First order kinetics.
- Square root of time vs.% CDR for Higuchi model;
- Log time vs Log% CDR for Kosemeyer Peppas model [9].

9. Stability Studies:

- The stability studies of the optimised formulation was carried out for 45 days in two different conditions at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH.
- These samples were analysed and checked for changes in physical appearance drug content and percent drug release at regular intervals [4,12].

RESULTS AND DISCUSSION

Phase Solubility Studies:

Discussion: The results of phase solubility are given in table-2. It was seen that solubility was found to be more in pH 6.8 buffer when compared to that of pH 7.4, it was selected as a dissolution medium.

Drug - Excipients compatibility studies by FT-IR:

Discussion: The FTIR spectra of the pure drug and polymers are given in figure-1 to 5 and table-3 shows the interpretation results. The FTIR spectra of combination of drug with the polymer did not show any changes in the characteristic peaks of the Candesartan cilexetil. The specific peaks at wave number 1751.54 cm^{-1} due to C=O stretching(ketone), 2862.14 cm^{-1} due to C-OH stretching (alcoholic), and C-N remain unchanged indicating that the drug had not interacted with the polymer.

DSC Studies

Discussion: Figure-6 and 7 shows the DSC thermograms of pure drug and optimised formula F3. The DSC thermogram of the pure drug candesartan cilexetil shows distinct endothermic peak at 174.67°C. The DSC analysis of the Optimised Formula (F3) revealed a negligible change from the endothermic peak of Candesartan Cilexitil.

Characterisation of Solid Dispersions and Physical Mixtures (Pms):

1.Drug Content and Solubility of SDs and PMs

Discussion: Results of drug content and solubility of SDs and PMs are given in Table-4. The drug content and solubility of the SD 1:3 ratios were found to be as optimised. Thus, solubility of the drug in water was increased successfully by preparing the solid dispersions.

2.*In Vitro* Drug Release of SDs and PMs:

Discussion: Results of *In Vitro* Drug Release of SDs And PMs are given in Table-5**.** The PMs and SDs of different ratios i.e 1:1, 1:2 and 1:3 were subjected to dissolution studies. The samples were withdrawn at specified time intervals and analysed with the help of a UV-Visible Spectrophotometer. The solid dispersions with 1:3 ratio were found to be optimised with 93.19±0.95% drug release after 60 mins. It was seen that as the amount of mannitol increased the release rate increased significantly.

Evaluation Parameters of Oral Disintegrating Film

Discussion: Results of various parameters weight variation, folding endurance, thickness, drug content, surface pH and disintegration time of oral disintegrating films are given in Table-6. The weight of the films of all batches were between 30mg to 36.5mg. A very low standard deviation value indicates that the method used was reproducible and consistent. The folding endurance of all the batches were found to be between 106.66±1.15 to 362.54 ±1.12. It was seen that batch with higher amount of polymer ratio scores higher folding endurance than the batch with lower polymer ratio. Drug content of all the films were between 85±1.52 to 93.75±1.63. The results of weight and % drug content showed that the film was homogenous and drug was also uniformly distributed in the films.

The thickness of F1 to F6 was found to be 0.13±0.02mm to 0.20±0.01mm. From the results obtained all formulations showed thickness of films as 5-200µm and complies with the limit as per the previous value. Films were having thickness adequate for handling and use. The disintegration time of all the batches (F1-F6) was found between 21.33±1.52 to 97.66±3.05. The formulation F3 was found to be as optimised as the disintegration time of F3 was found to be within the limit i.e 5-30 seconds as per specification (USP 2007). The disintegration times of the films were evaluated using phosphate buffer (pH6.8).

***In Vitro* Drug Release of Oral Disintegrating Films**

Discussion: Results of *In vitro*-Dissolution study of formulations F1 to F6 is given in Table-7**.** *In vitro* drug release studies were carried out by using USP dissolution apparatus type 1. The formulation F3 was selected as optimised formulation as drug release of F3 containing HPMC E5 200mg was found to be 98.91±0.73 within 10 mins which is more than the other formulations.

Study of Release Kinetics:

Discussion: Kinetic analysis of dissolution data is given in Table-8 and Figures- 10 to 13 represents Graphs indicating drug release kinetics of optimized formulation (F3)**.** When the data was subjected to zero order and first order kinetic model, a linear relationship was observed with high r^2 value for the zero-order model as compared to first order.

Stability Studies:

Discussion: Table – 9 and 10 represents Stability studies of Optimised Formulation F3 at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH. After a period of 45 days, the samples were observed for change in physical parameters. It was observed that surface was devoid of any change in color or appearance of any kind of spots on it. No change in the smoothness of the film were noted. The drug content and in vitro drug release were compared with initial profile to check the effect of storage on drug release of the formulation. Results from stability studies indicate that the formulated oral disintegrating films are stable and no remarkable changes were observed during the period of storage. The storage condition of 25±2°C/60±5% RH was better when compared to 40±2°C/75±5% RH.

Table-1: Formulation of Candesartan Cilexetil Films: (For 18 Films)

Composition (mg)	F1	F2	F3	F4	F5	F6
Drug: mannitol (1:3)	288	288	288	288	288	288
PVA	200	300	-	-	-	-
HPMC E-5			200	300	-	-
Sodium alginate	-	-	-	-	200	300
Croscarmellose sodium	10	10	10	10	10	10
Citric acid	20	20	20	20	20	20
Aspartame	1	1	1	1	1	1
Propylene glycol(ml)	2	2	2	2	2	2
Water	10	10	10	10	10	10

Table-2: Results of solubility

Solvents	Concentration (µg/ml)
Water	3.75±0.19
Methanol	110.31±0.57
6.8pH buffer	20.13±0.50
7.4pH buffer	11.29±0.50

Table-3: FT-IR interpretation of candesartan cilexetil

S.No	Functional Group	Frequency (cm^{-1})	Observed Peak(cm^{-1})
1	C-OH	2500-3300	2862.14
2	C=O	1670-1820	1751.54
3	C-N	1080-1360	1240.33

Table-4: Results of drug content and solubility of SDs and PMs

Drug: carrier	Drug Content (%)	Solubility(µg/ml)
PM (1:1)	80.63±0.87	11.36±0.50
PM (1:2)	78.8±0.95	17.12±0.40
PM (1:3)	80.45±0.84	24.78±0.67
SD (1:1)	82.25±0.87	18.33±0.30
SD (1:2)	81.39±0.78	23.62±0.37
SD (1:3)	87.72±0.96	31.36±0.34

All values are expressed in S.D (n=3)

Table-5: Results of cumulative %drug release of SDs and PMs:

Time(mins)	PM (1:1)	PM (1:2)	PM (1:3)	SD (1:1)	SD (1:2)	SD (1:3)
0	0.0	0.0	0.0	0.0	0.0	0.0
5	28.64±0.73	38.77±1.67	44.35±1.43	35.7±0.93	47.53±0.99	49.77±1.40
10	35.09±1.66	46.01±1.05	52.20±0.67	43.96±1.57	60.66±1.33	65.08±1.63
15	44.63± 1.92	55.22±1.63	60.78±0.12	52.67±1.85	66.72±1.63	72.38±1.68
30	55.71 ±1.30	66.66±0.76	69.23±0.43	58.87±1.98	76.33±1.77	81.72±1.97
45	64.03 ±1.64	72.43±1.14	77.05±0.26	65.98±1.17	83.70±0.38	89.57±1.22
60	68.58 ±1.23	79.38±1.91	86.34±0.32	71.32±1.90	90.44±0.74	93.19±0.95

All values are expressed in S.D (n=3)

Table-6: Results of various parameters of oral disintegrating films

Formulation Code	Weight variation(mg)	Thickness (mm)	Folding endurance	Surface pH	Disintegration time (secs)	Drug content (%)
F1	30±0.40	0.13±0.02	181.33±1.52	6.42±0.02	42.33±2.51	89.58±2.65
F2	36.5±1.54	0.17±0.01	183.34±1.42	6.32±0.02	53.66±4.04	86.66±1.90
F3	29±1.85	0.14±0.04	106.66±1.15	6.72±0.03	21.33±1.52	93.75±1.63
F4	35±1.42	0.18±0.01	133.66±1.52	6.71±0.07	30.66±1.15	87.16±1.04
F5	31±0.88	0.16±0.02	355.11 ±1.52	6.25±0.02	82.66±3.78	88.25±2.70
F6	36±1.57	0.20±0.01	362.54 ±1.12	6.54±0.02	97.66±3.05	85±1.52

All values are expressed in SD (n=3)

Table-7: Results of % cumulative drug release

Time (mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	46.79±0.72	42.32±1.39	48.63±0.30	42.95±0.54	40.66±0.58	34.17±0.65
4	59.91±0.91	53.69±0.82	60.44±0.89	56.36±0.51	57.07±0.13	49.83±0.67
6	70.33±0.77	65.73±1.08	71.97±0.48	69.58±0.42	69.87±0.11	67.65±0.37
8	83.41±1.22	77.73±0.92	86.13±0.25	80.29±0.67	81.58±0.55	79.99±0.10
10	91.77±0.99	89.92±0.76	98.91±0.73	93.36±0.41	90.32±0.62	85.94±0.55

All values are expressed in SD (n=3)

Table-8: Kinetic analysis of dissolution data

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.8368571	-0.166691	0.0328299	1.6904106
Intercept	16.829048	2.1559725	-0.027327	0.5327972
Correlation	0.9494899	-0.903096	0.9966704	0.8475848
R^2	0.901531	0.8155824	0.9933519	0.7184001

Table -9: Stability studies of Optimised Formulation F3 at 25 ± 2°C/60 ± 5% RH

Parameter	First day	30 days	45 days
Thickness(mm)	0.14±0.04	0.13±0.13	0.13±0.24
Folding endurance	106.66±1.15	105.66±0.25	105.66±1.10
Surface pH	6.72±0.03	6.72±0.03	6.72±0.03
%Drug content	93.75±1.63	92.14±0.12	92.19±1.02
In vitro %drug release	98.91±1.03	98.62±1.03	98.11±1.05

Table-10: Stability studies of Optimised Formulation F3 at 40 ± 2°C/75 ± 5% RH.

Parameter	First day	30 days	45 days
Thickness	0.14±0.04	0.12±0.23	0.12±0.32
Folding endurance	106.66±1.05	103.66±1.11	101.66±1.15
Surface Ph	6.72±0.03	6.72±0.03	6.72±0.03
Drug content	93.75±1.63	92.01±0.12	91.09±1.02
In vitro %drug release	98.91±1.03	97.42±1.03	97.01±1.05

Drug - Excipients compatibility studies by FT-IR:

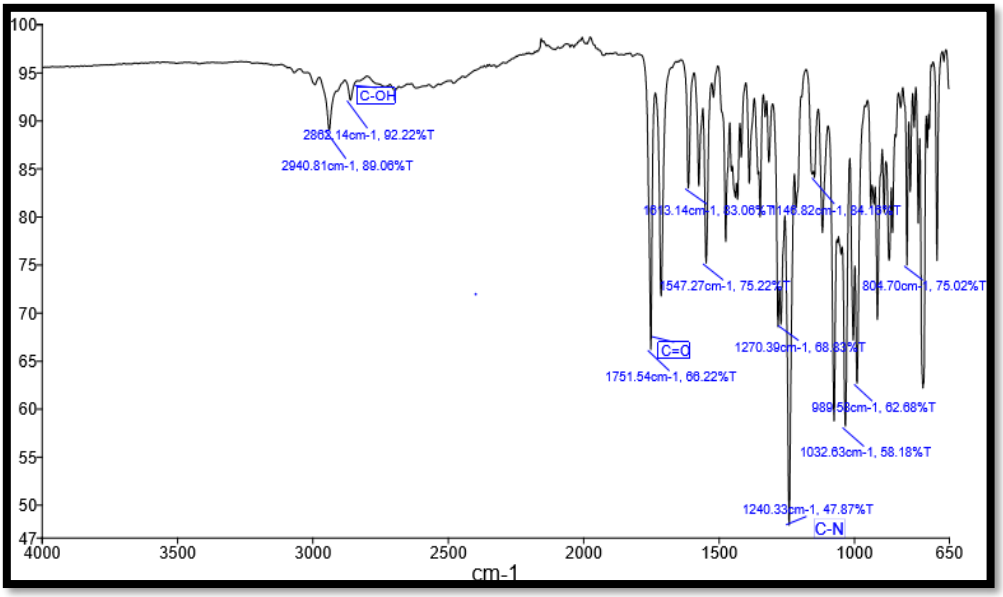

Figure-1: FT-IR of Pure Drug Candesartan Cilexetil

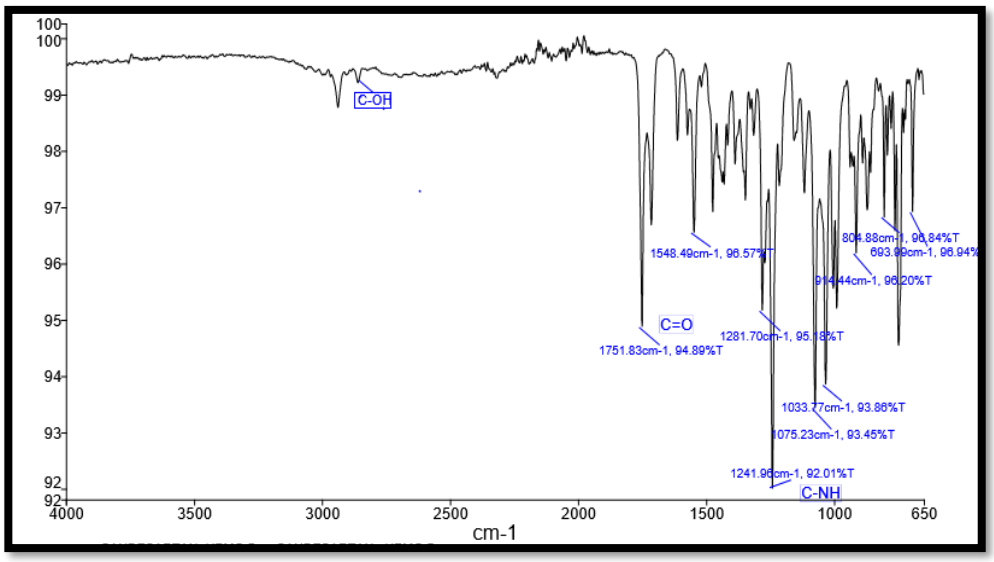

Figure-2: FT-IR OF Drug + HPMC E-5

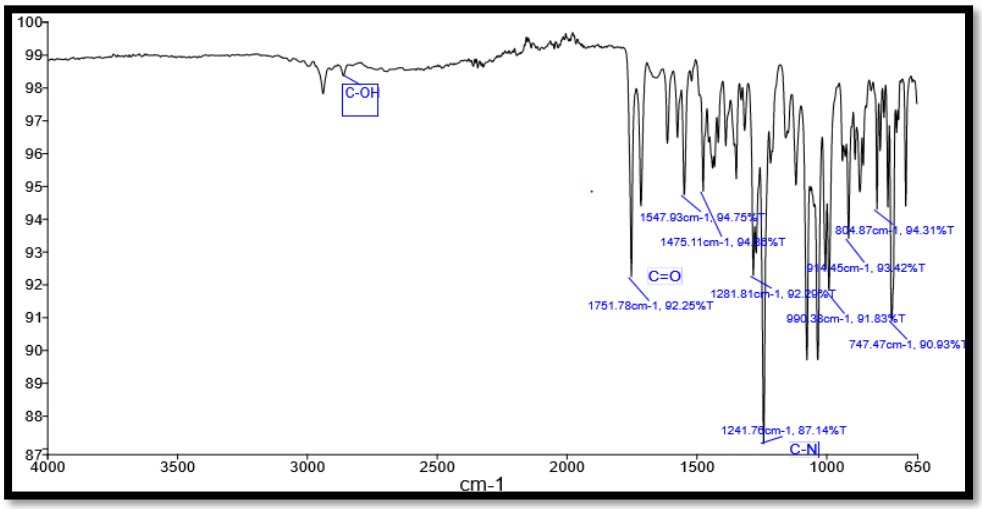

Figure-3: FT-IR of Drug + PVA

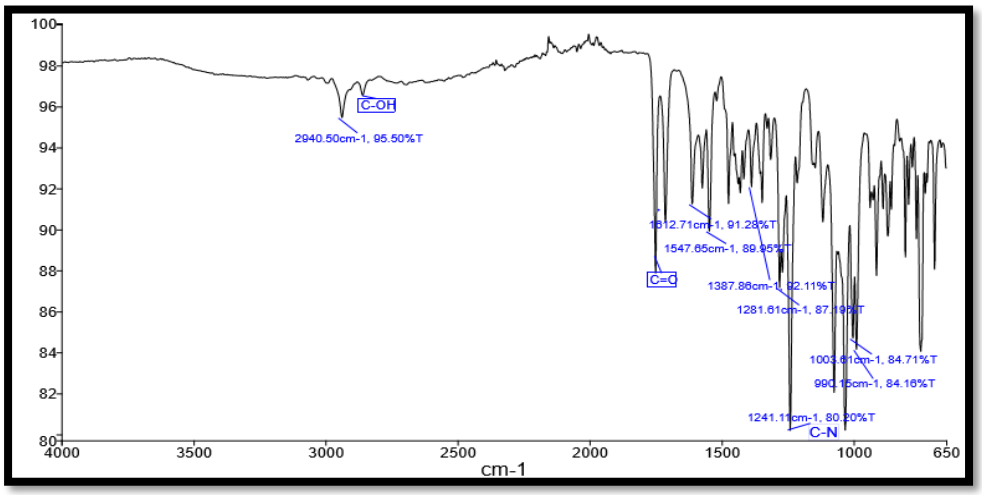

Figure-4: FT-IR of Drug + Sodium Alginate

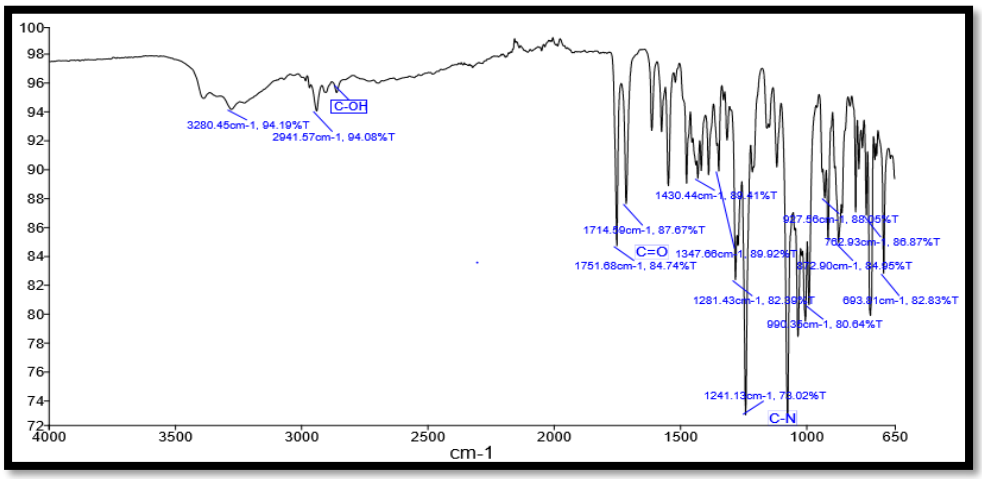

Figure-5: FTIR of Drug +Mannitol (Carrier)

DSC Studies

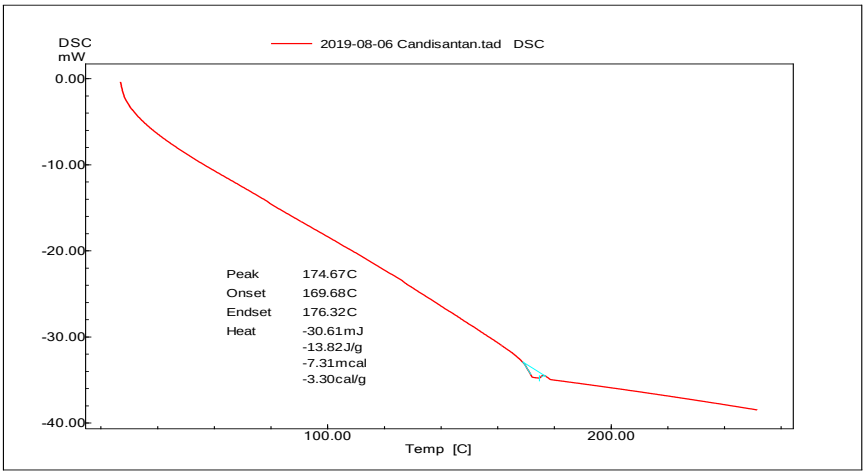

Figure-6: Thermogram of Candesartan Cilexetil (pure drug)

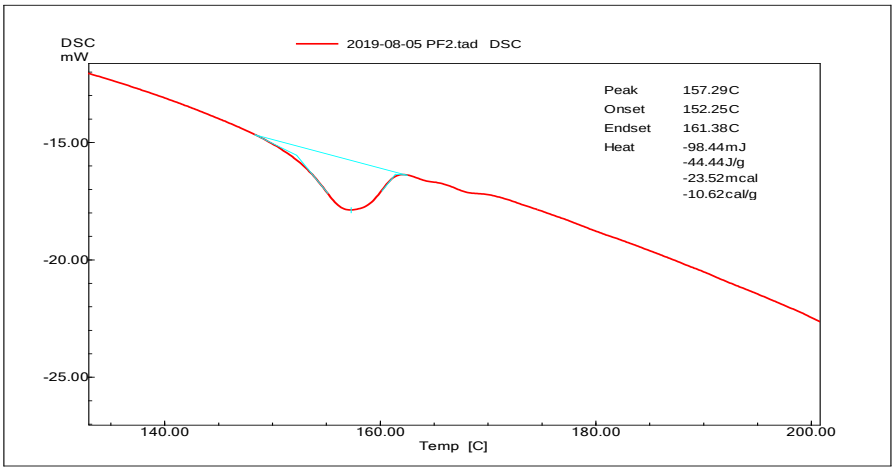

Figure-7: Thermogram of Optimised Formula (F3)

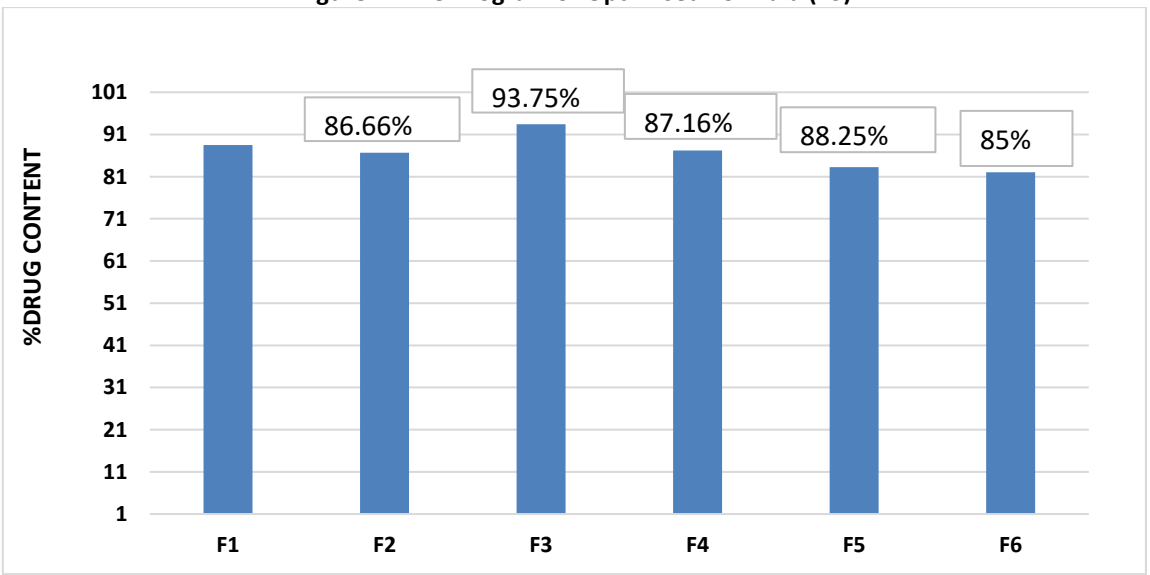

Figure-8: Graphical presentation of % drug content of formulations F1 to F6.

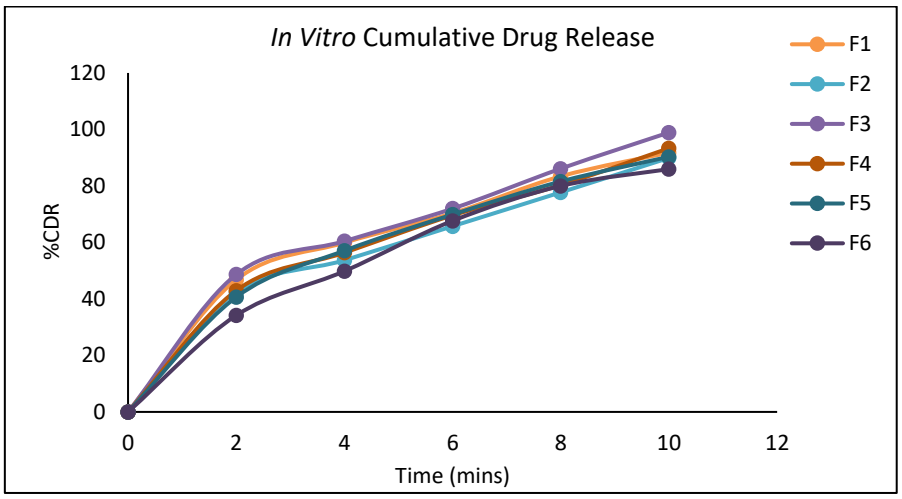

Figure-9: Comparative *In vitro*-Dissolution study of formulations F1 to F6.

CONCLUSION

The present investigation successfully formulated the oral disintegrating films of candesartan cilexetil. First the solid dispersions were prepared by fusion method to increase the solubility of the drug, then the films were formulated by solvent casting method using PVA, HPMC E5 and Sodium alginate as film forming polymers of different concentrations.

The FTIR and DSC studies revealed that there was no interaction found between the drug and the excipients.

Formulation F3 containing HPMC E5 200mg was selected as optimised formulation as the disintegration time was **21.33±1.52 secs** and in vitro drug release was **98.91±0.73** within 10 mins was better for F3 when compared to that of other formulations.

Further, long-term stability studies can be carried out and the study may be extended for assessing the *in vivo* release and in *vitro–in vivo* correlation. The future scope could be tested in human volunteers to evaluate bioavailability parameters.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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